Mechanics of the left ventricular myocardial interstitium: effects of acute and chronic myocardial edema

Ketaki V. Desai, Glen A. Laine, Randolph H. Stewart, Charles S. Cox, Jr., Christopher M. Quick, Steven J. Allen, and Uwe M. Fischer

Michael E. DeBakey Institute, Texas A&M University, College Station; and Center for Microvascular and Lymphatic Studies, University of Texas Medical School, Houston, Texas

Submitted 23 July 2007; accepted in final form 25 March 2008

Desai KV, Laine GA, Stewart RH, Cox CS Jr, Quick CM, Allen SJ, Fischer UM. Mechanics of the left ventricular myocardial interstitium: effects of acute and chronic myocardial edema. Am J Physiol Heart Circ Physiol 294: H2428–H2434, 2008. First published March 28, 2008; doi:10.1152/ajpheart.00860.2007.—Myocardial interstitial edema forms as a result of several disease states and clinical interventions. Acute myocardial interstitial edema is associated with compromised systolic and diastolic cardiac function and increased stiffness of the left ventricular chamber. Formation of chronic myocardial interstitial edema results in deposition of interstitial collagen, which causes interstitial fibrosis. To assess the effect of myocardial interstitial edema on the mechanical properties of the left ventricle and the myocardial interstitium, we induced acute and chronic interstitial edema in dogs. Acute myocardial edema was generated by coronary sinus pressure elevation, while chronic myocardial edema was generated by chronic pulmonary artery banding. The pressure-volume relationships of the left ventricular myocardial interstitium and left ventricular chamber for control animals were compared with acutely and chronically edematous animals. Collagen content of nonedematous and chronically edematous animals was also compared. Generating acute myocardial interstitial edema resulted in decreased left ventricular chamber compliance compared with nonedematous animals. With chronic edema, the primary form of collagen changed from type I to III. Left ventricular chamber compliance in animals made chronically edematous was significantly higher than nonedematous animals. The change in primary collagen type secondary to chronic left ventricular myocardial interstitial edema provides direct evidence for structural remodeling. The resulting functional adaptation allows the chronically edematous heart to maintain left ventricular chamber compliance when challenged with acute edema, thus preserving cardiac function over a wide range of interstitial fluid pressures.

left ventricular chamber compliance; compliance resetting; edemagenic gain

MYOCARDIAL INTERSTITIAL EDEMA can develop as a result of several clinical conditions such as acute and chronic arterial hypertension, acute and chronic pulmonary hypertension, acute coronary sinus hypertension, and interventions such as cardiopulmonary bypass and cardiac transplantation (10, 23, 24, 26, 27, 33, 34, 38). Edema develops in the left ventricle after elevation of right-sided heart pressures as a result of elevation of coronary venous and coronary microvascular pressures and, thus, increased microvascular filtration into the myocardial interstitium (29, 38). Acute myocardial edema is associated with increased stiffness of papillary muscle (11) and impairment of left ventricular systolic and diastolic function, including decreased left ventricular chamber compliance (10, 15, 27, 38, 42).

Models of chronic myocardial edema have been shown to induce development of myocardial interstitial fibrosis (27). Formation of left ventricular edema, after 2 mo of pulmonary artery banding in dogs, results in significantly increased interstitial collagen deposition in the myocardium of the left ventricular freewall (27). Chronic pulmonary artery banding in rats results in biventricular myocardial edema formation and increased myocardial mRNA levels of collagen types I and III within the left and right ventricular myocardium (9).

Interstitial fibrosis, developed in volume-overloaded and pressure-overloaded hearts (9, 27, 44, 45), is characterized by deposition of primarily type I collagen. This deposition results in diastolic dysfunction as observed by increased myocardial stiffness (12, 20), diminished ventricular chamber compliance (5), and slowing of ventricular relaxation (45). Collagen degradation and turnover (31, 32), as well as changes in collagen cross-linking (2, 36), could also have an effect on the physical properties of collagen and thus the myocardial interstitial matrix. However, the effect of myocardial interstitial fibrosis on ventricular mechanical properties appears to depend on the type of collagen deposited. A study (6) comparing rats with experimental arterial hypertension to chronically exercised rats showed evidence that a higher collagen III-to-collagen I ratio in the myocardium correlated with more rapid diastolic relaxation. How ventricular mechanical properties are affected by the type of collagen deposited during edema-induced interstitial fibrosis is not well described.

We therefore measured the end-diastolic pressure-volume relationship of both the left ventricular chamber and the left ventricular myocardial interstitium before and after acute edemagenic challenge in control animals and animals with chronically edematous hearts.

METHODS

Chronic Experimental Preparations

All procedures were approved by the Animal Welfare Committee at the University of Texas Medical School, Houston. Twenty six dogs of either sex with body weight >15 kg were used. Animals were anesthetized with 25 mg/kg thiopental sodium intravenously and intubated. Anesthesia was maintained with 0.5–1.5% halothane. Dogs were artificially ventilated with a respirator (Harvard Apparatus, South Natick, MA) set to deliver room air at a volume of 25 ml/kg and a rate appropriate to maintain PaCO2 between 35 and 40 mmHg. All
animals were allowed to recuperate for a period of 2 mo after surgery. Postoperative antibiotics and analgesics were administered by veterinarians as clinically indicated.

**Intramyocardial capsules.** Under sterile conditions, the chest was opened through a left lateral thoracotomy exposing the heart. The pericardium was opened exposing the left ventricular myocardium. Consistent with previous studies (29), solid-state pressure transducers (Millar, Houston, TX), encapsulated in porous polyethylene of 35-μm pore diameters, were inserted into the mid-myocardium of the left ventricle through blunt dissection. The final dimensions of the intramyocardial capsules were ~2 × 3 mm. The right ventricular myocardium is too thin to implanted our solid-state microtransducers, and thus the right ventricular pressure-volume relationship cannot be determined using this technology. To facilitate the measurement of myocardial interstitial fluid pressure, three capsules were placed in each left ventricular myocardium ensuring that at least one of the transducers would be operational 2 mo after implantation for use in the acute protocols. Consistent with previous studies (29), the pericardium was not surgically reapproximated. Solid-state pressure transducers were used in place of fluid-filled catheters to obtain higher fidelity (rise time <20 ms) recordings of myocardial interstitial hydrostatic pressure due to the constantly changing interstitial pressures associated with myocardial contraction (29). Myocardial interstitial fluid pressure varies as a function of myocardial contraction, reaching a minimum during diastole. As a result, maximum left ventricular transmicrovascular fluid flow occurs during diastole. We therefore expressed our results in terms of myocardial interstitial fluid pressure and volume recordings obtained at end diastole (29). Catheters from the solid-state pressure transducers were exteriorized through the thoracotomy and coiled into a subcutaneous pouch. The chest was closed with a multiple layer technique, and the animals were allowed to recuperate. A total of 18 animals was instrumented with interstitial fluid pressure monitoring capsules.

**Pulmonary artery banding.** In 11 animals, pulmonary arterial pressure was elevated by pulmonary artery banding to create chronic myocardial edema. Copper wire was encased in polyethylene tubing to minimize erosion and scarring and was then placed around the pulmonary artery during the sterile surgical preparation. Unlike studies (4) where the pulmonary artery was progressively occluded to mimic a model of progressive pulmonary artery stenosis, we banded the pulmonary artery to maintain a fixed reduction in diameter and a fixed mean pulmonary artery pressure of between 30 and 35 mmHg (8, 37, 47). With chronic body fluid redistribution, pulmonary artery pressure tended to decrease over time, although it was sufficiently elevated in all animals to produce the desired level of myocardial edema accumulation. An increase in pulmonary artery pressure results in an increase in pressure within the Thebesian veins and coronary sinus. This elevates microvascular pressure within the left ventricle, thus potentiating left ventricular myocardial edema. Elevation of right-sided circulatory pressures and superior vena caval pressure in this model also reduces the volume of cardiac lymph that can flow into the central venous circulation, thus further potentiating myocardial edema (28). This model produces right-sided pressures within the heart and vasculature analogous to those seen in right heart failure or cor pulmonale (28). The chest was closed as indicated in Intramyocardial capsules, and animals were allowed to recuperate for a period of 2 mo.

**Acute Experimental Preparations**

Animals were anesthetized, intubated, and ventilated as described in our chronic surgical preparation. Vascular lines were placed to constantly monitor arterial and venous pressures. The myocardium was exposed through a left thoracotomy as described previously.

**Coronary sinus pressure elevation.** A pressure-monitoring Swan-Ganz balloon-tipped catheter (Edwards Laboratories, Santa Ana, CA) was inserted through the right jugular vein and directed into the right atrium. The catheter was then advanced into the coronary sinus and sutured to the external wall of the sinus in such a manner as to not occlude the vessel. Mean pressure within the coronary sinus was recorded from the Swan-Ganz catheter. When the Swan-Ganz catheter balloon was inflated, graded elevations in coronary sinus pressure could be obtained. The affixing suture ensured that the balloon could not be ejected from the coronary sinus. With coronary sinus pressure elevation, microvascular pressure within the myocardium increases, potentiating the rate at which fluid enters the myocardial interstitium. Coronary sinus pressure was thus elevated in a stepwise fashion in control dogs and in those with chronic myocardial edema to potentiate edema formation and compromise cardiac function (29).

**Left ventricular myocardial interstitial fluid pressure.** The chronically implanted Millar catheters were exteriorized from their skin pouch and connected to Millar amplifiers and recorders. Viewed microscopically, the porous polyethylene capsules were found to be encased in loose connective tissue surrounded by normal myocytes with no visible signs of inflammation or scarring. Each catheter was tested to determine the fidelity of its myocardial interstitial fluid pressure measurements. Compression of the tissue over the catheters produced a high-fidelity change in myocardial interstitial fluid pressure. A second test occasionally used was acutely changing the circulating colloid osmotic pressure either through hemodilution or colloid administration. All these interventions manifest themselves through changes in myocardial interstitial fluid pressure. Any catheter not responding appropriately was not used (30). Since myocardial interstitial fluid pressure can be affected by external or internal compression, myocardial left ventricular interstitial fluid pressure at end diastole \(P_{\text{INT}}\) was normalized. This normalized value was expressed as \(P_{\text{INT}}\) minus left ventricular end-diastolic chamber pressure. Except during left ventricular volume infusion to determine left ventricular chamber compliance, the baseline left ventricular end-diastolic chamber pressure was not elevated in our chronic preparation and did not change during the course of our experiments.

**Left ventricular chamber compliance.** Left ventricular volume was determined by insertion of an Edwards impedance catheter through the aorta into the left ventricular chamber. A Millar solid-state pressure transducer was also introduced into the left ventricle to measure left ventricular end-diastolic chamber pressure along with a catheter for volume infusion. We then infused isotonic saline directly into the left ventricle at a rate that increased left ventricular end-diastolic chamber pressure by 7–8 mmHg in each animal. Unlike intravenous volume transfusion, right-sided vascular pressures (coronary sinus pressure) did not change during volume infusion. After a stable elevated left ventricular end-diastolic chamber pressure was maintained for 5 min, left ventricular end-diastolic chamber volume was again determined three times. We calculated left ventricular chamber compliance as the change in left ventricular end-diastolic chamber volume \(\Delta EDV\) divided by the change in left ventricular end-diastolic chamber pressure \(\Delta EDP\).

\[
\text{left ventricular chamber compliance} = \frac{\Delta EDV}{\Delta EDP} = \frac{EDV_2 - EDV_1}{EDP_2 - EDP_1} (1)
\]

where \(EDV_1\) is the initial left ventricular end-diastolic chamber volume, \(EDP_1\) is the initial left ventricular end-diastolic chamber pressure, \(EDV_2\) is the left ventricular end-diastolic chamber volume after saline infusion, and \(EDP_2\) is the left ventricular end-diastolic chamber pressure after saline infusion. Because the ventricular pressure-volume curve is nonlinear, the slope or compliance varies with location on the curve. Therefore, all compliance determinations in each animal were made starting at the same end diastolic pressure. At the conclusion of each protocol, animals were euthanized with an overdose of thiopental sodium and 20 ml of saturated potassium chloride solution.

**Wet weight-to-dry weight ratio (myocardial edema).** The amount of myocardial edema or extravascular fluid (EVF) was obtained from the
unitless blood free (wet weight–dry weight)/dry weight ratio for the left ventricular myocardium. After removal of tissue for collagen digestion and histological analysis of porous polyethylene capsules, all of the remaining left ventricular myocardium was homogenized. A spectrophotometric correction for blood volume was performed since the volume of blood and consequently water found within the coronary vasculature may vary throughout the course of an experiment (25). The homogenate was then weighed and dried to a constant weight. We (27) have previously demonstrated that this procedure quantifies extracellular, EVF volume changes or myocardial interstitial edema since cellular volume remains constant. Control myocardial EVF values obtained during the left ventricular chamber compliance protocol were determined by transmural myocardial biopsy (once in control animals before generating acute edema), after which cardiac tissue was placed in a (kersone/bromobenzene) gradient column to determine percent water and EVF (17, 27). The myocardial interstitial pressure-volume relationship was expressed as EVF, i.e., myocardial EVF was designed to simulate patients with chronic right heart failure or pulmonary disease, which elevates right-sided circulatory pressures, thus potentiating myocardial edema (28).

Protocol 2: determining the effect of chronic myocardial edema on left ventricular chamber compliance. GROUP 2A. In five animals, left ventricular chamber compliance was calculated before and after left ventricular myocardial edema formation was potentiated by coronary sinus pressure elevation.

GROUP 2B. In three animals with chronic myocardial edema secondary to pulmonary artery banding, left ventricular chamber compliance was determined at baseline and after additional acute myocardial edema formation.

Statistical Analysis

All data are means ± SE. Normalized left ventricular end-diastolic interstitial fluid pressures and myocardial EVF values were compared using either a Student’s t-test or a paired t-test. A P value <0.05 was considered significant. Regression equations were calculated using the least squares method (35). The coefficients of the regression equations representing the slopes and y-axis intercepts were compared using Student’s t-test (35).

RESULTS

Table 1 summarizes the experimental interventions performed in each group along with the measured parameters. In brief, subjects in groups 1a and 2a did not have pulmonary artery banding and chronic myocardial edema. GROUP 1a was used as baseline, and left ventricular end-diastolic interstitial fluid pressure and myocardial EVF were measured. In group 1a controls, left ventricular end-diastolic interstitial fluid pressure and myocardial EVF were measured before and after acute myocardial edema formation. Left ventricular chamber compliance was calculated for group 2a before elevation of coronary sinus pressure. It was calculated again after the generation of acute myocardial edema. Subjects in groups 1b and 2b had their pulmonary artery banded to induce chronic myocardial edema. Left ventricular end-diastolic interstitial fluid pressure and myocardial EVF were measured for group 1b, and left ventricular chamber compliance was calculated for group 2b.

Table 1. Distribution of subjects in experimental groups

<table>
<thead>
<tr>
<th>Protocol 1</th>
<th>No Pulmonary Artery Banding Group 1a</th>
<th>Pulmonary Artery Banding Group 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular end-diastolic interstitial fluid pressure-volume (extravascular fluid) relationship</td>
<td>Baseline: 48 historic controls and 2 new controls for validation (n = 50)</td>
<td>Control animals: left ventricle made chronically edematous (n = 3)</td>
</tr>
<tr>
<td></td>
<td>Control animals: left ventricle made acutely edematous by coronary sinus pressure elevation (n = 8)</td>
<td>Chronically edematous: left ventricle made acutely edematous by coronary sinus pressure elevation (n = 5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protocol 2</th>
<th>No Pulmonary Artery Banding Group 2a</th>
<th>Pulmonary Artery Banding Group 2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular chamber compliance</td>
<td>Control animals: left ventricle made acutely edematous by coronary sinus pressure elevation (n = 5)</td>
<td>Chronically edematous: left ventricle made acutely edematous by coronary sinus pressure elevation (n = 3)</td>
</tr>
</tbody>
</table>
Additional acute myocardial edema was then generated in all chronically edematous animals, with the exception of control animals with chronic edema, and all measurements were repeated.

Normalized values of left ventricular end-diastolic interstitial fluid pressure as a function of myocardial EVF are illustrated in Fig. 1. In control animals (group 1a: baseline, n = 50) at a baseline myocardial EVF value of 2.9 ± 0.07 [wet weight−dry weight]/dry weight, normalized left ventricular end-diastolic interstitial fluid pressure was 14.9 ± 1.1 mmHg. Elevating coronary sinus pressure resulted in the formation of acute myocardial edema (group 1a: control animals, n = 8), which manifests itself as an increase in myocardial EVF, plotted as a function of myocardial extravascular fluid (EVF) [wet weight−dry weight]/dry weight, indicating the degree of myocardial edema.

Figure 1. Normalized left ventricular end-diastolic interstitial fluid pressure plotted as a function of myocardial extravascular fluid (EVF) [wet weight−dry weight]/dry weight, indicating the degree of myocardial edema. The normalized value was calculated as the recorded myocardial left ventricular interstitial fluid pressure at end diastole minus left ventricular end-diastolic chamber pressure. Controls made acutely edematous by coronary sinus pressure elevation. Animals with chronic edema (group 1b: control animals, n = 3) was significantly higher than the myocardial EVF value of subjects in group 1a at baseline. We compared the normalized values of left ventricular interstitial fluid pressure at end diastole in control animals with acute edema (37.5 ± 1.8 mmHg) to animals with chronic edema (22.2 ± 1.4 mmHg; group 1b: chronically edematous, n = 5). At a myocardial EVF value of 3.5 ± 0.03, normalized left ventricular end-diastolic pressures in the two sets of animals were significantly different (P < 0.01). Generation of acute edema in chronically edematous subjects also increased the normalized left ventricular end-diastolic interstitial fluid pressure values from 22.2 ± 1.4 mmHg at control to 45 ± 2.4 mmHg (P < 0.01) at an EVF of 3.6 ± 0.04. It is interesting to note that further increasing myocardial EVF > 3.5 did not increase normalized left ventricular end-diastolic interstitial fluid pressure in animals with chronically edematous hearts.

Figure 2 demonstrates left ventricular chamber compliance plotted as a function of myocardial EVF. Regression lines were plotted for control data (y = −4.11x + 15.64; r² = 0.67) and chronic myocardial edema data (y = −4.70x + 20.73; r² = 0.86). In control animals (group 2a: control animals, n = 5), compliance was determined at baseline and after acute edema formation. All compliance determinations in each animal were made starting at the same end diastolic pressure by altering end diastolic volume. The negative slope of the regression line demonstrates that left ventricular chamber compliance decreased in animals made acutely edematous, indicating that hearts became stiffer. Animals with chronic edema (group 2b: chronically edematous, n = 3), after pulmonary artery banding, also demonstrated a decrease in left ventricular chamber compliance when compliance was determined both before and after they were made acutely edematous, also indicated by the negative slope of the regression line. The slopes of the control regression line and the chronic edema regression line could not be shown to be significantly different (35). Before generation of acute edema, left ventricular chamber compliance was higher in chronically edematous animals compared with non-
edematous animals.

Myocardial collagen content in the control group 1a was 3.9 ± 0.44 mg/100 mg dry wt and 5.8 ± 0.34 mg/100 mg dry wt in the chronic edema group 1b, demonstrating a significant difference. The distribution of left ventricular collagen changed when animals were made chronically edematous; the percentage of type III collagen increased from 11% in control animals to ~90% in animals with chronic edema, while the percentage of type I collagen decreased from 85 to ~10%.

Figure 3 illustrates left ventricular chamber compliance as a function of the normalized left ventricular end-diastolic interstitial fluid pressure. Left ventricular chamber compliance values were obtained by substituting myocardial EVF values from Fig. 1 into regression equations from Fig. 2. Standard deviations for left ventricular chamber compliance were also computed from regression equations from Fig. 2. We placed boundary limits on the lower values of myocardial EVF to avoid negative or nonphysiologic values for left ventricular chamber compliance (see Fig. 3). Left ventricular chamber compliance was lower in acutely edematous animals (1.24 ml/mmHg) at the normalized left ventricular end-diastolic interstitial fluid pressure value of 37.5 ± 1.8 mmHg, compared with nonedematous control animals (3.71 ml/mmHg) at 14.9 ± 1.1 mmHg. Animals with chronic edema demonstrated a higher control value of left ventricular chamber compliance (4.27 ml/mmHg) compared with nonedematous control animals (3.71 ml/mmHg). Even after left ventricular end-diastolic interstitial pressure was acutely elevated in chronically edematous animals to 45 mmHg, the left ventricular chamber compliance value remained relatively high at 3.8 ml/mmHg. As illustrated in Fig. 3, the points representing animals with chronic edema are shifted to the right, indicating a more compliant myocardium at any given left ventricular end-diastolic interstitial fluid pressure.
Myocardial Interstitium

Pressure-Volume Relationship of Acutely and Chronically Edematous Left Ventricular Myocardial Interstitium

This study is the first to characterize the pressure-volume relationship of the left ventricular myocardial interstitium subjected to acute and chronic edema. Animals subjected to an acute increase in myocardial EVF or myocardial edema exhibit an increase in stiffness of their left ventricular myocardial interstitium. However, when animals with chronic myocardial edema were subjected to acute edemagenic conditions, their pressure-volume relationships demonstrated a right shift in the curve compared with control animals with acute edema (Fig. 1). In other words, generating acute myocardial interstitial edema in control animals resulted in an increase in left ventricular end-diastolic interstitial fluid pressure, which was significantly higher than that resulting from a comparable increase in myocardial EVF in animals with chronic edema. The pressure-volume relationships were plotted by joining data points linearly and not as regression lines (Fig. 1). If the curves were plotted nonlinearly, there would still be a right shift for animals with chronic myocardial edema. We were confident that increasing myocardial EVF to ~3.5 [(wet weight–dry weight)/dry weight] would raise myocardial left ventricular end-diastolic interstitial fluid pressures. However, an additional increase in myocardial EVF did not raise left ventric-ular end-diastolic interstitial fluid pressure beyond ~50 mmHg in either acute or chronic conditions. We speculate that damage to the interstitial matrix (which may or may not be reversible) may have occurred. We anticipated that the curve would break in the opposite direction resulting in significantly elevated interstitial pressures for relatively small increases in volume. We believe that when capillary pressure increases to ~50 mmHg after coronary sinus pressure elevation, there is enhanced venous outflow from the Thebesian veins (18, 19) into the right ventricle where the pressure is relatively lower. Opening of the lower resistance Thebesian outflow limits the elevation in myocardial microvascular pressure, and thus left ventricular end-diastolic interstitial fluid pressure, from exceeding ~50 mmHg. An alternate explanation is that the heart may attempt to decrease interstitial pressure by shunting fluid across the myocardial surface (transudation). This would keep interstitial pressure at a lower level and eliminate the potential for microvascular collapse and cardiac death. Another explanation is that the myocardium is not homogeneous and, at higher pressures, fluid may be accumulating in places other than where the transducers were recording pressures.

Pressure-Volume Relationship of Acutely and Chronically Edematous Left Ventricular Chamber

Acutely elevating the myocardial interstitial fluid content of the left ventricular interstitium resulted in decreased compliance of the left ventricular chamber in both nonedematous control and chronically edematous animals. We hypothesized that left ventricular chamber compliance would be lower and the left ventricle would be stiffer in chronically edematous animals under control conditions. However, chamber compi-
ance of hearts with chronic myocardial edema was higher under control conditions compared with nonedematous hearts. The information presented in Fig. 3 was derived from the data in Fig. 1 substituted into the regression equations of Fig. 2, determined using the methods of least squares. Because this does not always result in a perfect fit (as indicated by the $r^2$ values), it was possible for slightly negative values for compliance to be computed. This concept is called to the reader’s attention, since negative compliance values have no physiologic meaning and simply represent a statistical anomaly. Increases in pulmonary artery pressure similar to those observed in our pulmonary artery banding model have been shown to increase right ventricular volume and, via ventricular interdependence, shift the intraventricular septum towards the left ventricle. Acutely, this shift in the ventricular septum can increase left ventricular chamber stiffness. The observation that the left ventricle in our study appeared more compliant after chronic edema suggests that the effect of chronic edema may be much greater than that of potential ventricular interdependence.

**Interstitial Fibrosis and Chronic Edema**

The quantity of interstitial fibrosis in the heart can be estimated by the amount of collagen in the myocardial interstitium. Myocardial collagen is comprised primarily of types I, III, and V, with type I collagen predominating (20). Characteristics of the type of collagen play a marked role in determining the behavior of the myocardial interstitium. While type I collagen is composed of larger diameter fibers with greater stiffness, type III collagen is relatively more distensible with small diameter fibers (5, 20). Since fibrillar type I collagen is relatively stiff, small changes in its content can affect the functional properties of the heart. It has been hypothesized that the increased collagen content, and not left ventricular mass, during systemic hypertension results in diastolic dysfunction (5, 21). This could be attributed to an increase in the collagen type I-to-type III ratio, which could be responsible for the increased stiffness of the left ventricle (46). Increased collagen deposition in the heart can be attributed to increased collagen expression in response to variations in hemodynamic loading (7). Depending on the response of the heart to these mechanical stimuli, cardiac fibroblasts may activate different signal transduction pathways to regulate the fibrotic content of the myocardium (1). Thus, hypertensive hearts responded to pressure overload resulting in increased collagen type I concentration and a stiffer myocardium. Type I collagen fibrosis predominates in the left ventricular myocardium exposed to an increased afterload. The right ventricle also hypertrophies when challenged by an elevated vascular outflow pressure (pulmonary artery pressure; Ref. 37) similar to how the left ventricle responds to systemic arterial hypertension (12). We speculate that in a model of pulmonary artery hypertension, the right ventricle, exposed to pressure overload, would have an elevated collagen type I-to-type III ratio. We did not perform analysis of the right ventricle in our study due to physical constraints in implanting the porous polyethylene capsules. However, it would be interesting to know if right ventricular fibrosis with type I collagen takes place in our model of pulmonary artery hypertension (increased right ventricular afterload). When our animals were made chronically edematous (with no pressure overload), type I collagen was replaced by type III collagen. Because collagen has a rapid turnover (31, 32), it would be unlikely to observe any transient changes in the type after 2 mo. Increased distensible type III collagen may be responsible for the increased left ventricular chamber compliance in chronically edematous hearts. We have previously demonstrated a similar increase in compliance and interstitial distensibility or decreased stiffness of the small bowel in conjunction with gastrointestinal edema (39, 41). The concept of “compliance resetting” in chronic disease has also been addressed in the bioengineering literature (13, 14, 16).

**Adaptive Remodeling of the Heart**

Banding of the pulmonary artery and generation of chronic myocardial interstitial edema resulted in structural adaptation or remodeling of the left ventricle. Although we did not conduct any studies to characterize a causal relationship between changes in collagen degradation or cross-linking and adaptive remodeling of the heart, we did observe a shift in the primary collagen type in the left ventricle from type I to III. For a given left ventricular end-diastolic interstitial fluid pressure (Fig. 3), chronically edematous hearts had higher left ventricular chamber compliance compared with nonedematous or acutely edematous hearts. We believe that patients with chronically edematous hearts are better equipped to cope with certain pathological conditions (10, 26, 27, 33, 34, 38) associated with acute edema formation compared with patients with nonedematous hearts. This change in left ventricular chamber compliance could be attributed to the distensible fibers of collagen type III that were laid down during the development of chronic myocardial edema in these animals. The concept of adaptive remodeling of the interstitium to regulate compliance has been previously demonstrated in several models (13, 14, 16, 23, 24, 39–41).

Adaptive remodeling of the chronically edematous myocardial interstitium could result from factors other than a shift in predominant collagen type. To assess structural changes in the myocardial interstitial matrix, collagen biochemistry, including studies of concentration, types, ratios, turnover, and degradation (31, 32) as well as changes in cross-linking (2, 36), would be valuable. Our protocols were designed primarily to evaluate myocardial interstitial matrix mechanics. A future study could be designed to evaluate collagen biochemistry and histology of not only the left ventricle, which could provide an alternative explanation for the shift in myocardial interstitial pressure-volume relationship, but also of the right ventricle, which has not been adequately characterized. Samples of the right and left ventricle could be taken on a daily or weekly basis, because of the rapid rate of collagen degradation and turnover (31, 32), during the development of myocardial edema and interstitial fibrosis. However, due to high costs associated with chronic canine studies and the significant numbers required to track biochemical changes over shorter time intervals (to detect changes in degradation and cross-linking), a rat model may be more appropriate. Such studies would, however, preclude evaluation of interstitial mechanics.

**GRANTS**

 Portions of this work were supported by National Heart, Lung, and Blood Institute Grant HL-36115, National Institute of General Medical Sciences Grant GM-00675, Centers for Disease Control Grant CCU-623086, and the American Heart Association.
REFERENCES


